Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 59 p. (Technology appraisal guidance; no. 316).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

- Enzalutamide is recommended within its marketing authorisation as an option for treating metastatic hormone-relapsed prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy, only if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.
- The use of enzalutamide for treating metastatic hormone-relapsed prostate cancer previously treated with abiraterone is not covered by this guidance.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Metastatic hormone-relapsed prostate cancer

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Internal Medicine

Oncology

Urology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen

Target Population

Adults with metastatic hormone-relapsed prostate cancer whose disease has progressed during or after docetaxel-containing chemotherapy

Interventions and Practices Considered

Enzalutamide

Major Outcomes Considered

- Clinical effectiveness
  - Rate of pain palliation
  - Overall survival
  - Radiographic progression-free survival
  - Modified progression-free survival
  - Time to first skeletal-related event
  - Objective response rate (the proportion of patients with a complete or partial radiographic response)
  - Prostate-specific antigen (PSA) response rate
  - Adverse events
  - Health-related quality of life
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Searches

An evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), developed by McGowan et al. was used to inform this critique. The submission was checked against the single technology appraisal (STA) specification for manufacturer/sponsor submission of evidence. The ERG has presented only the major limitations of each search strategy in the main report. Further criticisms of each search strategy can be found in Appendix 1 in the ERG report (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Searches were reported for the majority of databases required by NICE, except Medline in Process (see Sections 6.1 and 10.2 in the manufacturer's submission [MS]). The ERG queried this omission in their clarification letter and asked if this resource was included in the EMBASE/Medline search. In the response to the clarification letter, the manufacturer indicated that Medline in Process has been included in PubMed. This has been checked on the website of the National Library of Medicine (NLM) and identified as correct.

The MS included a simultaneous search of multiple databases (EMBASE and Medline searched at the same time) using a single host and search strategy. This type of search has limitations which could affect recall of results, such as reliance on the use of MeSH terms only.

The ERG noted the following significant errors in the manufacturer's searches:

- The ERG noted that the EMTREE terms for enzalutamide and cabazitaxel were not included in the EMBASE search. As a result, relevant results may have been missed.
- The search was confused and inadequate. The intentions of the searcher were unclear. The line combinations were muddled and the use of subheadings excessively restrictive.

The ERG noted errors in the documentation for the following search strategies (see Section 10.2 in the MS):

- The search of the Cochrane Library appeared to use PubMed syntax, which would have failed to retrieve relevant references correctly from the Cochrane Library via the Wiley interface. This was queried by the ERG in the clarification letter. In the response to clarification, the manufacturer stated that Cochrane had been searched via Wiley. The ERG tried to replicate the manufacturer's search strategy in the Cochrane Library (via Wiley) using the syntax provided by the manufacturer; however, the strategy resulted in errors and failed to run.

The manufacturer reported that additional searches were undertaken in Google and for conference abstracts; however, search strategies were not provided for these resources. The ERG requested these strategies in the clarification letter, and full strategies were subsequently supplied by the MS in their response. Due to the transitory nature of the content retrieved by Google searches, the ERG did not attempt to replicate these searches.

Indirect and Mixed Treatment Comparisons

The manufacturer stated that the clinical effectiveness searches in Section 6.1.1 in the MS would be used to inform the mixed treatment comparison. Therefore additional strategies were not included in this section.

Non-Randomised Controlled Trial (RCT) Evidence

The MS reported that no relevant non-RCTs were identified during a systematic literature review (SLR) conducted by Quintiles (see Section 6.8 in the MS). The SLR was published in June 2013 but included exactly the same search strategies and errors as the industry submission. It appears

that minor changes were unintentionally introduced by auto-correction changes made by Microsoft WORD in the NICE submission. The manufacturer decided not to include strategies for non-RCTs in the submission, due to lack of results in the SLR. The search strategy used in the SLR (Table 14.1 in the MS) used ineffective and confused filters and this may have resulted in missing relevant studies.

Adverse Events

The manufacturer stated that searches for adverse events were already covered by the clinical effectiveness search. The Centre for Reviews and Dissemination (CRD) guidance recommends that if searches have been limited by an RCT filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. Despite the addition of a systematic review filter, the ERG considered that it was possible that some relevant evidence may not have been identified as a consequence of the restrictive study design limit.

Cost-effectiveness

Searches were reported for the majority of databases required by NICE, except Medline in Process (Section 10.10.4 in the MS). The manufacturer stated that the Database of Abstracts of Reviews of Effects (DARE) and the National Health Service Economic Evaluation Database (NHS EED) were searched through the Cochrane Library. However, it was not stated if the Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Central Register of Controlled Trials (CENTRAL) were also included. The ERG requested this information in the clarification letter. The manufacturer replied in their clarification response that Medline in Process was included in the PubMed search and that CENTRAL and CDSR were included in the Cochrane library search.

The ERG noted errors in the documentation for the following search strategies in this section (Section 10.10 in the MS):

- The ERG noted that the lines in Table 103 in the MS were incorrectly numbered and queried this in the clarification letter. The manufacturer responded with an amended search strategy with corrected line numbers.
- The economics search of the Cochrane Library appeared to use PubMed syntax, which would have failed to retrieve relevant references correctly from the Cochrane Library via the Wiley interface. This was queried by the ERG in the clarification letter. In the response to clarification, the manufacturer stated that Cochrane had been searched via Wiley. The ERG tried to replicate the manufacturer's search strategy in the Cochrane Library (via Wiley) using the syntax provided by the manufacturer; however, the search resulted in an error message and failed to run.
- The strategy included an unused "orphan" line (#6) which was not combined for the final search results. This may have resulted in missing important references.

Measurement and Valuation of Health Effects

The MS reported that the measurement and valuation of health effects analysis (Sections 7.4.5 and 10.12 in the MS) was informed by the search for cost-effectiveness. Therefore no additional strategies were included in this section.

The ERG noted errors in the documentation for the following search strategies in Section 10.12 in the MS:

- In the EMBASE/Medline search strategy in Table 103 in the MS, the lines after #15 were confused, attempting to erroneously combine lines which were not present in the strategy. The ERG asked for a corrected version in the clarification letter, which was provided in the manufacturer's response. The manufacturer's response also included a change in the final line of this search strategy. This change resulted in 20 new results which might not have been included in the manufacturer's review process.
- As discussed in the previous section, the Cochrane Library strategy appeared to employ PubMed syntax rather than the appropriate Wiley Cochrane Library syntax. The ERG attempted to re-run this search however the strategy resulted in an error message and failed to run or retrieve references. Furthermore, line 6 was a redundant orphan line and was not included in the final result. This may have resulted in the omission of results.

Resource Identification, Measurement and Valuation

The MS reported that the resource identification, measurement and valuation section (Sections 7.5.3 and 10.13 in the MS) was informed by the search for cost effectiveness. No additional strategies were included in this section.

Summary of Searching

The searches documented in the initial manufacturer's submission contained several areas of weakness, only those relating to reproducibility were included in the clarification letter forwarded to the manufacturer by NICE. The manufacturer addressed all the points of concern raised by the ERG in their response to the clarification letter.

Inclusion Criteria

The eligibility criteria used in the search strategy are described in the table below. The eligibility criteria used in the search strategy are in line with the NICE scope.

Table. Eligibility Criteria Used in Search Strategy

	Clinical Effectiveness
Inclusion criteria	Population: mCRPC that has progressed on or after docetaxel treatment Interventions: enzalutamide, abiraterone (plus prednisone or prednisolone), mitoxantrone (plus prednisone or prednisolone) Outcomes: OS, PFS, ORR, PSA response, time to first SRE, TTD, AEs Study design: randomised or non-randomised studies with two or more arms Language restrictions: none
Exclusion criteria	Population: patients not in the post-chemotherapy setting Interventions: studies that did not include at least one of the interventions of interest Outcomes: studies that did not assess at least one of the outcomes of interest Study design: case studies Language restrictions: none

Abbreviations: AE: adverse events; mCRPC: metastatic castrate-resistant prostate cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PSA: prostate-specific antigen; SRE: skeletal-related events; TTD: time to treatment discontinuation.

Cost-effectiveness

ERG Comment on Manufacturer's Review of Cost-effectiveness Evidence

A full systematic review was carried out by the manufacturer to identify relevant cost-effectiveness studies. The quality of the search strategy is discussed above and in Chapter 4.1.1 of the ERG report (see the "Availability of Companion Documents" field).

Objective of Cost-effectiveness Review

The main objective of the cost effectiveness review was to retrieve relevant data from published literature regarding the cost-effectiveness of enzalutamide and relevant comparators as outlined in the scope. The search strategy for relevant economic studies was detailed in Appendix 10, Section 10.10 of the MS. The databases searched were PubMed/MEDLINE, Cochrane Library (including DARE and NHS EED databases), EMBASE, EconLit, HTA Watch (81), HEED, Medline (R) In-Process, Conference proceedings (ISPOR). All searches were conducted on 2 January 2013 and covered the period between 1 January 1993 and 1 January 2013. The search was limited to the year 2012 for conference abstracts. A description of the search strategies is given in Appendix 10, Section 10.10 of the MS.

Inclusion/Exclusion Criteria Used in the Study Selection

The inclusion criteria were according to the population, intervention, comparator, outcomes, study design (PICOS) criteria reported in the table below. Exclusion criteria were: any studies not meeting the PICOS criteria (see table below). The ERG views that the inclusion and exclusion criteria used in the study selection are appropriate.

Table. PICOS Strategy for Studies on Cost-effectiveness

Population	Adults with metastatic castration-resistant prostate cancer which has been previously treated with a docetaxel-containing chemotherapy regimen
Intervention*	Enzalutamide, abiraterone in combination with prednisone or prednisolone, mitoxantrone alone or in combination with prednisolone.
Comparator*	• Abiraterone in combination with prednisone or prednisolone • Mitoxantrone alone or in combination with prednisolone • Cabazitaxel alone or in combination with prednisolone • Best supportive care (this may include radiotherapy, radiopharmaceuticals, analgesics, bisphosphonates, further hormonal therapies, and corticosteroids)
Outcomes	• Quality-adjusted life-years (QALYs); Life-years gained (LYG) • Incremental cost-effectiveness ratios (ICERs) such as cost per QALY
Study design	[illegible]

	• Full economic evaluations, i.e., comparative analyses including enzalutamide and/or any of the other interventions in terms of both costs (resource use) and consequences (outcomes) that use cost-effectiveness analyses, cost-utility analyses or cost-benefit analyses • Partial economic evaluations, i.e., cost analyses, cost comparison studies or cost-outcome descriptions of any intervention against any comparator

*No specific search for these interventions or comparators was conducted, but only those studies including these agents in the economic comparisons were reviewed.

ERG Comment

The ERG views that the inclusion and exclusion criteria used in the study selection are appropriate.

Number of Source Documents

Clinical Effectiveness

11 relevant studies were identified. Only two of the 11 studies identified were considered relevant for the decision problem in this single technology appraisal: the AFFIRM trial and the COU-AA-301 trial. The other nine studies were excluded as they were not linked to the intervention of interest: enzalutamide.

Cost-effectiveness

The systematic literature review identified six economic evaluations directly related to the decision problem. None of the studies in the economic review included enzalutamide as a comparator. For this reason the manufacturer has provided a de novo analysis.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of Data Extraction

One randomised controlled trial (RCT) was included for enzalutamide, the AFFIRM trial. The data from this trial were extracted from five publications: the published journal article by Scher et al., 2012, the full clinical study report for the AFFIRM trial, two American Society of Clinical Oncology (ASCO) abstracts, and a report from Quintiles describing patient reported outcomes in the AFFIRM trial.

In addition, one trial was included for abiraterone, the COU-AA-301 trial. The data from this trial were extracted from five publications: two

published journal articles by De Bono et al. 2011 and Fazizi et al. 2012, and three ASCO abstracts.

Quality Assessment

The quality assessments of both the AFFIRM and COU-AA-301 studies can be found in Table 4.2 in the ERG report (see the "Availability of Companion Documents" field).

The methods used to generate random allocation sequence and for concealment of allocation sequence were reported for both studies and were judged as adequate. Blinding status was clear for both studies and neither of the studies showed any evidence of selective reporting. Overall, neither of the two studies used in the indirect treatment comparison (ITC) were identified as being at a high risk of bias.

ERG Comment

The ERG agrees with the manufacturer's assessment that neither of the two studies used in the indirect comparison were at a high risk of bias.

Evidence Synthesis

The same search and inclusion criteria (see table in the "Description of Methods Used to Analyze the Evidence" field) were used for the systematic literature review (SLR) for the indirect and mixed treatment comparison as for the SLR for the intervention. Based on the searches, 11 relevant studies were identified. These trials are described in Table 4.3 in the ERG report (see the "Availability of Companion Documents" field).

The network of RCT evidence identified by the SLR is described in Figure 4.1 in the ERG report (see the "Availability of Companion Documents" field).

Only two of the 11 studies identified were considered relevant for the decision problem in this single technology appraisal (STA): the AFFIRM trial and the COU-AA-301 trial. The other nine studies were excluded as they were not linked to the intervention of interest: enzalutamide. The COU-AA-301 trial was included because an indirect comparison was deemed feasible when the comparator arms in AFFIRM and COU-AA-301 were considered similar. However, the treatment received in both comparator arms differed in:

- Proportion of patients exposed to prednisone: 100% in the placebo arm of COUAA-301 versus 45.6% in the placebo arm of AFFIRM.
- Reason for the need of corticosteroids: to avoid toxicity in COU-AA-301 and supportive treatment in AFFIRM.

The placebo arm in COU-AA-301 (100% of patients on prednisone) was assumed to have the same treatment outcomes as the placebo arm in AFFIRM.

The MS does not present effectiveness results for mitoxantrone which was identified as one of the comparators in the NICE final scope. All trials including mitoxantrone were excluded from the MS. In the economic model for the abiraterone STA (TA-259), evidence for the effectiveness of mitoxantrone was either based on the per protocol (PP) arm of the COU-AA-301 trial or on data from the TROPIC study:

- The overall survival (OS) under mitoxantrone was taken to be equal to the PP arm of the COU-AA-301 trial.
- Progression free survival (PFS) was modelled on treatment discontinuation of the per protocol (PP) arm.
- Treatment discontinuation was based on an analysis of the TROPIC study.

An overview of the TROPIC study is presented in Section 4.5 in the ERG report (see the "Availability of Companion Documents" field).

ERG Comment

The MS does not provide details of what constituted best supportive care (BSC) in the two trials (AFFIRM and COU-AA-301). Therefore, the ERG asked the manufacturer to define BSC in both trials. According to the manufacturer "Best supportive care (BSC) in AFFIRM and COU-AA-301 studies encompassed the following:

- In AFFIRM: radiopharmaceuticals, analgesics, bisphosphonates, hormonal therapies and corticosteroids. Radiotherapy was also considered as BSC however, in AFFIRM when radiotherapy was given this was reported as a skeletal related event (SRE) event.
- In COU-AA-301: radiotherapy, bisphosphonates, analgesics and LHRH agonists as needed. In this study, all patients received corticosteroids as part of the study medication. Similarly to AFFIRM, radiotherapy was considered as BSC but when administered, this was reported as a SRE event."

Refer to Section 4 in the ERG report for additional information on the clinical effectiveness review (see the "Availability of Companion Documents" field).

Cost-effectiveness

An overall summary of the de novo economic model developed by the manufacturer is given in Table 5.3 in the ERG report (see the "Availability of Companion Documents" field).

Model Structure

The structure of the Markov state transition model follows the structures used in numerous NICE STAs and multiple technology assessments (MTA) in metastatic cancer. It includes three health states: Stable Disease (SDis), Progressive Disease (PDis) and Dead (see Figure 5.1 in the ERG report [see the "Availability of Companion Documents" field]). The assumed cycle length is three weeks (mainly chosen based on previous models in the same indication) and the time horizon is 10 years (assumed to be sufficient to capture the remaining lifetime of metastatic castrate-resistant prostate cancer [mCRPC] patients). Metastatic CRPC patients enter the model in the SDis state after their disease has progressed on or after chemotherapy. They remain in this health state as long as they remain alive and progression free. Patients who die move to the dead health state, whilst patients who progress move to the PDis health state. From the PDis health state, patients may either remain alive in the PDis health state, or die and move to the dead health state. The number of people remaining in each health state after each cycle in the best supportive care (BSC) strategy was calculated from the overall survival (OS) and time to treatment discontinuation (TTD; as a proxy for progression-free survival [PFS]) curves from the placebo arm in the AFFIRM trial. Time in the postprogression state was calculated as the difference between OS and PFS. The enzalutamide and abiraterone strategies were modelled by applying HRs to the survival curves. The analysis took a National Health Service and personal social services perspective and discounted costs and benefits at 3.5%.

Refer to Section 5 of the ERG report for additional information on the manufacturer's economic model and to Table 6.1 in the ERG report for an overview of additional and exploratory analyses undertaken by the ERG.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions on the Evidence for Cost-effectiveness

Availability and Nature of Evidence

The Committee was aware that the evidence presented by the manufacturer in its original submission related to the overall population (that is, patients who had received 1 or more cytotoxic chemotherapy regimens). The Committee concluded that it could make a recommendation for patients who had received 1 cytotoxic chemotherapy regimen based on the evidence for the overall population. However, for patients who had received 2 or more cytotoxic chemotherapy regimens, it concluded that it could not make a recommendation without data on the baseline expected survival and a robustly modelled incremental cost-effectiveness ratio (ICER) for these patients.

The Committee acknowledged the additional evidence provided by the manufacturer for the subgroup of patients who had received 2 or more previous courses of cytotoxic chemotherapy. It was aware that this subgroup was prespecified in AFFIRM's study protocol and represented around 27% of the total trial population. The Committee was aware that patients in AFFIRM had not received previous treatment with abiraterone.

The Committee had not been presented with sufficient evidence to inform a decision on the clinical- or cost-effectiveness of the sequential use of enzalutamide after abiraterone.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee agreed that the rigid criteria for stopping treatment in COU-AA-301 may have biased the overall survival end point against abiraterone and introduced uncertainty. The Committee concluded that, given that the survival benefit of abiraterone is unlikely to vary in clinical practice, assuming a constant hazard ratio over the entire time horizon would be the most plausible scenario to model overall survival for abiraterone.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The Committee appreciated that a larger sample would have reduced uncertainty around the EuroQOL 5 dimension (EQ-5D) utility value used in the model at baseline; however, it agreed that the sample was adequate compared with those used in previous appraisals in the same disease area.

The Committee noted that the manufacturer applied different 'on-treatment' increases in utility for enzalutamide and abiraterone. The Committee, noting the patient experts' experience, agreed that including 'on-treatment' utility increases reflected patient experience, but that there was no evidence to assume different values for enzalutamide and abiraterone. The Committee concluded that the modelling should incorporate equal utility increases for both treatments.

The Committee agreed that the utility decrease for disease progression applied by the manufacturer in the model did not represent the decrease in utility experienced by patients whose disease had progressed in AFFIRM. Without another more robust value of the utility decrease for disease progression, it concluded that the value used by the manufacturer could be considered appropriate.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

The Committee considered enzalutamide for patients who had received 1 course of cytotoxic chemotherapy separately from patients who had received 2 or more courses of cytotoxic chemotherapy.

What Are the Key Drivers of Cost-effectiveness?

The Committee noted that the method used to model overall survival for abiraterone is key to the cost-effectiveness of enzalutamide compared with abiraterone.

Most Likely Cost-effectiveness Estimate (Given as an ICER)

For patients who had received 1 previous cytotoxic chemotherapy regimen, the Committee noted that the analysis reflecting its preferred assumptions, but not the actual patient access scheme discount for abiraterone, gave an ICER of £22,600 per quality-adjusted life year (QALY) gained for enzalutamide compared with abiraterone. The Committee agreed that enzalutamide would remain cost-effective when the correct patient access scheme for abiraterone is taken into account.

For patients who had received 2 or more previous courses of cytotoxic chemotherapy, the Committee noted that the ICER estimated by the manufacturer for enzalutamide compared with best supportive care was £45,500 per QALY gained and that the ERG's ICER was £48,000 per QALY gained.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of enzalutamide and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from randomised controlled trials. For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen

Potential Harms

- The summary of product characteristics states that if severe toxicity or an intolerable adverse reaction occurs after taking enzalutamide, treatment should be stopped for 1 week or until symptoms improve, then resumed at the same or a lower dose (120 or 80 mg/day). The dose of enzalutamide should also be reduced if a drug that inhibits cytochrome P (CYP) 2C8 is administered at the same time.

- The summary of product characteristics lists the following common adverse reactions to enzalutamide: headache, hot flushes, falls, bone fractures, hallucinations, anxiety, dry skin, itching, hypertension, low white blood cell count, memory impairment and difficulty thinking clearly. It advises caution when administering enzalutamide to people with a history of seizures or other predisposing factors for seizures, such as underlying brain injury, stroke, brain tumours or brain metastases, or alcoholism. For full details of adverse reactions, see the summary of product characteristics.

Contraindications

Contraindications

For full details of contraindications, see the summary of product characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. Implementation of this guidance is the responsibility of local commissioners and/or providers.
- Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Service (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has metastatic hormone-relapsed prostate cancer and the doctor responsible for their care thinks that enzalutamide is the right treatment, it should be available for use, in line with NICE's recommendations.
- The Department of Health and the manufacturer have agreed that enzalutamide will be available to the NHS with a patient access scheme which makes enzalutamide available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the Commercial Manager at the manufacturer directly on 0203 379 8773 or email – commercial@astellas.com.
- NICE has developed a costing statement (see also the "Availability of Companion Documents" field) explaining the resource impact of this guidance, to help organisations put this guidance into practice.

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 59 p. (Technology appraisal guidance; no. 316).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2014 Jul

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen. Costing statement. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. 1 p. (Technology appraisal guidance; no. 316). Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site .
- Riemsma R, Joore MA, Tomini F, Deshpande S, Ramaekers BLT, Worthy G, Hilmer D, Armstrong N, Severens JL, Kleijnen J. Enzalutamide for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen: a single technology appraisal. York (UK): Kleijnen Systematic Reviews Ltd; 2013 Oct. 149 p. Electronic copies: Available from the NICE Web site .

Patient Resources

The following is available:

- Enzalutamide for metastatic hormoneâ€‘relapsed prostate cancer previously treated with a docetaxelâ€‘containing regimen. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jul. (Technology appraisal guidance; no. 316).

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site. Also available for download as a Kindle or EPUB ebook from the NICE Web site.

NGC Status

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